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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/979,539	11/20/2001	Ira Pastan	15280-3951US	5936

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/979,539	PASTAN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *41-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40 and 51-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 April 2005 has been entered.

2. Claims 1-66 are pending.

Claims 1-5, 27, 30; 33, 51-53, 60 and 64 have been amended.

Claims 41-50 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. Claims 1-40 and 51-66 are under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. The rejection of claims 1-21, 27-29 and 33-40 under 35 U.S.C 112, second paragraph for indefiniteness is withdrawn in view of the amendments to the claims.

7. The rejection of claim 21 under 35 U.S.C 112, first paragraph as not complying with the written description requirement is withdrawn in view of the amendments to the claim.

8. The rejection of claims 6-7, 11, 17-20, 22-26, 35, 51-62 and 64-66 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims is withdrawn in view of applicant's arguments.

9. The rejection of claims 1-7, 12-40, 51-55 and 57-66 under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims is withdrawn in view of the amendments to the claims.

10. The rejection of claims 1-6, 8-21, 27-28, 31-34, 36-37, 39-40, 51-54, 56-61, 63-64 and 66 under 35 U.S.C. 103(a) as being unpatentable over Chowdhury et al [a] in view of Wagner et al and Pastan et al and Adams et al is withdrawn in view of applicant's arguments.

New Grounds of Objections/Rejections

11. Claims 7 and 63 objected to because of the following informalities:

a. Claim 7 is objected to because there is a space in the word "substitution s" that does not belong.

b. Applicant is advised that should claim 31 be found allowable, claim 63 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Appropriate correction is required.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 1-6, 27-28, 51-54 and 60-61 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-6, 27-28, 51-54 and 60-61, as written, do not sufficiently distinguish the claimed polypeptides and nucleic acids over antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed antibodies and the naturally occurring antibodies. Naturally occurring antibodies in vivo undergo affinity maturation by somatic hypermutation, which does not occur randomly, but is preferentially targeted to hot spot motifs frequently located in the CDRs. Thus, the instant claims drawn to polypeptides and nucleic acids encoding polypeptides comprising a VH and VL having at least one amino acid substitution in a CDR at a hot spot motif read on naturally occurring antibodies.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1996)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F. Supp 68 (1967), 155 U.S.P.Q. 139, (District Court, New Jersey, 1967)). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

14. Claims 1-40 and 51-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-21, 27-29, 31-40 and 51-59 are indefinite for reciting "having at least 5 times higher binding affinity for an antigen bound by a parental antibody" in claims 1, 27 and 33 and for reciting "having at least 5 times higher binding affinity for an antigen bound by SS antibody than does SS antibody" in claim 51. The phrase "having at least 5 times higher binding affinity for an antigen bound by a parental antibody" is unclear because the claimed polypeptide comprising a VH and VL which binds the same antigen and only differs from the parental antibody by mutations/substitutions in at least one CDR hot spot is reasonably expected to share a common epitope with the parental antibody. Thus, if the antigen is already bound to the parental antibody, it is unclear if the claimed polypeptide comprising a VH and VL would also bind. Does the claimed polypeptide displace the parental antibody and bind the antigen with 5 times higher affinity, or does the claimed polypeptide bind a different epitope than the parental

antibody or does the 5 times higher binding affinity require that the antigen be bound to the parental antibody or is the increased binding affinity of the claimed polypeptide simply relative to the binding affinity of the parental antibody for the same antigen? Similarly, the polypeptide of claim 51, which comprises a VH and VL chain and only differs from the SS antibody by mutations/substitutions in at least one CDR hot spot is reasonably interpreted to share a common epitope with antibody SS. As above, it is unclear if the phrase "having at least 5 times higher binding affinity for an antigen bound by SS antibody than does SS antibody" means that antibody SS and the claimed polypeptide binds a different epitope or if the increased affinity of the claimed polypeptide requires that the antigen be bound by antibody SS or does the claimed polypeptide displace the antigen bound by antibody SS such that it can bind with 5 times higher affinity? As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. Applicant may overcome this rejection by amending the claims to recite "having at least 5 times higher binding affinity for an antigen relative to the affinity of the parental antibody for the same antigen" or similar language, provided that no new matter is added.

b. Claims 33-37 are indefinite because the claims recite a method of killing a malignant cell bearing an antigen comprising contacting the cell with an immunotoxin, however, the claims do not state whether the antigen targeted by the polypeptide comprising a VH and VL (i.e., targeting moiety of the immunotoxin) is the same antigen as that expressed on the malignant cells. The claims only refer to the polypeptide comprising a VH and VL in terms of its higher affinity for an antigen relative to the

affinity of a parental antibody for the same antigen and it is unclear if the "an antigen" is the same as that expressed on the malignant cells. The claims do not state that the targeting moiety of the immunotoxin bind the antigen expressed on the malignant cells.

c. Claims 31-32 and 63 recite the limitation "a nucleic acid molecule". There is insufficient antecedent basis for this limitation in the claim. Claims 31-32 and 63 depend from claim 27 or claim 28, which are drawn to a single nucleic acid molecule. Thus, the recitation of "a nucleic acid molecule" rather than "the/said nucleic acid molecule" implies that there are multiple nucleic acid molecules and it is unclear if the nucleic acid recited in base claims 27 or 28 is the nucleic acid referred to in dependent claims 31-32 and 63.

d. Claims 6-7, 9, 11, 17-20, 22-26, 28-30, 32, 35-40, 51-62 and 64-66 are indefinite in the recitation of "SS antibody" in claims 6, 22, 28, 30, 35, 51, 54, 60-61and 64-65 and "antibody E4" in claim 38 as the sole means of identifying the antibody. The use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct molecules. This rejection can be obviated by amending the claims to specifically and uniquely identify "SS antibody" and "antibody E4", for example, by SEQ ID number.

e. Claims 6-7, 9, 11, 17-20, 22-26, 28-30, 32, 35-40, 54-55, 61-62 and 65 are indefinite because the claims recite amino acid substitutions at specific positions in antibody SS, however, the claims do not define the complete sequence of the SS antibody. Further, the specification, which identifies antibody SS as a single-chain

antibody represented by SEQ ID NO:1 (see Fig. 1), does not contain the specific amino acid residues at the positions recited in the clams. For example, claim 6 recites that the polypeptide may differ from antibody SS by an amino acid substitution of at least one amino acid selected from S92, G93 and Y94 in CDR3 of the light chain (see claim 2). However, SEQ ID NO:1, the light chain begins with the sequence DIQLT (residues 136-140) meaning that residue 92 is glycine, residue 93 is tyrosine and residue 94 is proline, however, claim 6 recites that residue 92 is serine, residue 93 is glycine and residue 94 is tyrosine. Additionally, claims 22 and 30 recite an amino acid substitution in the light chain CDR3 of antibody SS of at least L96T, however, according to SEQ ID NO:1 residue 96 of the light chain is threonine and not a leucine residue. Which sequence is correct and is SEQ ID NO:1 the reference sequence? Further, the claims recite "SS1", "D8" and "C10" in parenthesis (e.g., see claim 7), which are not defined by the claims. As stated above, the use of laboratory designations to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct molecules.

15. Claims 1-6, 8-21, 27-28, 31-34, 36-37, 51-54, 56-61, 63-64 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowdhury et al (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998, cited previously on PTO-892 mailed 11/6/03) and Wagner et al (Nature 376: 732, 31 August 1995, cited previously on PTO-892 mailed 11/6/03) and Schier et al (Journal of Molecular Biology, 263:551-567, 1996) and Pastan

et al (U.S. 6,083,502, 102(e) date 1/12/1998, cited previously on PTO-892 mailed 11/6/03).

The claims are interpreted as being drawn to a polypeptide comprising a VH and VL, the polypeptide having at least 5 times higher binding affinity for an antigen relative to the affinity of the parental antibody (i.e., antibody SS) for the same antigen, wherein the polypeptide has a sequence that differs from the parental antibody by an amino acid substitution of at least one amino acid in a CDR, the amino acid in the parental antibody being encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW and wherein the substitution occurs in CDR3 of the light or heavy chain variable region or wherein the substitution occurs in CDR1 or CDR2 of the light or heavy chain variable region and the polypeptide is a scFv, a dsFv, a Fab or a F(ab)2 and the polypeptide further comprises a detectable label or therapeutic moiety that is a toxic moiety, which is a *Pseudomonas* exotoxin that is PE38 or wherein the toxic moiety is selected from diphtheria toxin, saporin, pokeweed antiviral toxin, ricin or bryodin 1 or cytotoxic fragments thereof and the polypeptide may be expressed in conjunction with surface protein gIIIp of a filamentous bacteriophage. The claims are also drawn to nucleic acids encoding said polypeptide and a method of killing malignant cells bearing an antigen (mesothelin) comprising contacting the cell with the polypeptide immunotoxin comprising PE35, PE38 or PE40.

Chowdhury et al teach anti-mesothelin antibody SS (SS scFv) conjugated to PE38 and methods of killing malignant cells with the SS scFv-PE38 immunotoxin. Chowdhury et al teach anti-mesothelin antibodies that were not useful because of low

affinity and poor internalization (see page 669, right column). Chowdhury et al teach that a scFv, a dsFv, or a Fab can be fused in-frame with the minor surface protein gIIIp of the filamentous phage (see page 670, left column). Chowdhury et al teach the isolation of SS scFv, which binds with high affinity to mesothelin and the SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors (see pages 671-674). Chowdhury et al do not teach hot spot sequence motifs, or mutating CDR hot spots for targeted affinity maturation or that increased affinity leads to improved selective tumor delivery or other types of anti-mesothelin antibodies such as Fab, $F(ab)_2$, or dsFvs and immunotoxins thereof other than *Pseudomonas* endotoxin (PE). These deficiencies are made up for in the teachings of Wagner et al and Schier et al and Pastan et al.

Wagner et al teach hot spot serine codons AGY in the CDRs and TCN codons in the frameworks of human V gene segments. Wagner et al teach the consensus sequence [A/G,G, C/T,A/T] as a preferred target for mutation and most hot spots are associated with AGY serine codons. Wagner et al teach that biased serine codon usage in immunoglobulins has evolved to help the somatic hypermutation machinery target CDRs and thus, mutations are targeted to residues that could yield increased affinity and away from sites that are more likely to destroy the structural scaffolding.

Schier et al teach that restriction of mutagenesis to the CDRs located at the center of the antibody combining site of a scFv that targets the tumor antigen c-erbB-2 produces scFv affinities in the low nanomolar range (average scFv affinity was 3.6nM) and the in vitro affinity maturation of the c-erbB-2 scFv was observed to mimic somatic

hypermutation in vivo, which targets specific sequence hotspots intrinsic to the mutational process (see page 553, right column, Tables 2-4 and pages 560-561 and Figure 5). Schier et al teach that very high affinity antibody fragments significantly increase tumor retention and the scFv can be used as a building block to create dimeric scFv, with yet higher apparent affinity due to avidity, and even greater tumor retention (see page 562, right column).

Pastan et al teach the mesothelin antigen and methods for targeting and/or inhibiting growth of cells bearing mesothelin (i.e. malignant cells) (see abstract). Pastan et al teach the K1 antibody (see columns 28-32) and methods of using anti-mesothelin antibodies (Fv, dsFv, Fab, $F(ab)_2$, single-chain antibody) to target cytotoxins such as PE, DT, ricin and abrin to mesothelin expressing cells (see columns 15-18).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of

Chowdhury et al and Wagner et al and Schier et al and Pastan et al because Chowdhury et al teach that the SS scFv binds with high affinity to mesothelin and SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors whereas other anti-mesothelin antibodies with low affinity and poor internalization (i.e., mAb K1) were not useful for targeted therapy and Wagner et al teach hot spot motifs AGY and [A/G,G, C/T,A/T] and hot spot mutations are targeted to residues that could yield increased affinity and are away from sites that are more likely to destroy the structural scaffolding and Scheir et al teach that in vitro affinity maturation of an antibody fragment (c-erbB-2 scFv) was observed to mimic somatic hypermutation in vivo, which targets specific sequence hot spots intrinsic to the mutational process and this affinity maturation yielded affinities in the low nanomolar range or lower (i.e., picomolar). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al because Pastan et al teach the mesothelin antigen and antibody (K1) methods for targeting and inhibiting growth of cells (i.e. malignant cells) bearing mesothelin (see abstract) with cytotoxins such as PE, DT, ricin and abrin. Therefore, it would have been obvious to one of ordinary skill in the art to efficiently increase the affinity of the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) by

targeting mutations to CDR hot spots and away from residues that may destroy the structural scaffold and hence, its antigen-binding function and one of ordinary skill in the art would have been motivated to increase the affinity for increased tumor targeting and retention for therapeutic benefit of mesothelin expressing tumors. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-6, 8-21, 51-54 and 56-59 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-31 of U.S. Patent No. 6,809,184 B1 as evidenced by Figure 1 in view of Chowdhury et al (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998, cited previously on PTO-892 mailed 11/6/03) and Wagner et al (Nature 376: 732, 31 August 1995, cited previously on PTO-892 mailed 11/6/03) and Schier et al (Journal of Molecular Biology, 263:551-567, 1996) and Pastan et al (U.S. 6,083,502, 102(e) date 1/12/1998, cited previously on PTO-892 mailed 11/6/03).

The instant claims and their interpretation have been described supra.

Claims 1-7 and 9-31 of U.S. Patent No. 6,809,184 B1 are drawn to an isolated anti-mesothelin antibody comprising a VH chain and/or a VL chain as set forth in SEQ ID NO:5 or comprises the CDRs as set forth in SEQ ID NO:5 or comprises the framework regions as set forth in SEQ ID NO:5 and the antibody is a scFv or a dsFv and is labeled with a detectable label or is attached or fused to a therapeutic agent that is a toxin and is *Pseudomonas* exotoxin or cytotoxic fragment thereof. The claims of U.S. Patent No. 6,809,184 B1 do not specifically teach increasing the affinity of the anti-mesothelin antibody or antibody SS comprising mutating at least one CDR hot spot, wherein the hot spot motif is selected from AGY or RGYW or a Fab or F(ab)2 or the toxic moieties PE38, diphtheria toxin, saporin, pokeweed antiviral toxin, ricin or bryodin 1 or cytotoxic fragments thereof or expression in conjunction with surface protein gIIIp of a filamentous bacteriophage. These deficiencies are made up for in the teachings of Chowdhury et al and Wagner et al and Schier et al and Pastan et al.

Chowdhury et al have been described supra.

Wagner et al have been described supra.

Schier et al have been described supra.

Pastan et al have been described supra.

The claims in the instant application are obvious variants of claims 1-7 and 9-31 of U.S. Patent No. 6,809,184 B1 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al because Chowdhury et al teach that the SS scFv binds with high affinity to mesothelin and SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors whereas other anti-mesothelin antibodies with low affinity and poor internalization (i.e., mAb K1) were not useful for targeted therapy and Wagner et al teach hot spot motifs AGY and [A/G,G, C/T,A/T] and hot spot mutations are

targeted to residues that could yield increased affinity and are away from sites that are more likely to destroy the structural scaffolding and Scheir et al teach that in vitro affinity maturation of an antibody fragment (c-erbB-2 scFv) was observed to mimic somatic hypermutation in vivo, which targets specific sequence hot spots intrinsic to the mutational process and this affinity maturation yielded affinities in the low nanomolar range or lower (i.e., picomolar). As evidenced by Figure 1 of U.S. patent 6,809,184, antibody SS (scFv) of Chowdhury et al necessarily comprises the VH-linker-VL sequence of SEQ ID NO:5. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Pastan et al because Pastan et al teach the mesothelin antigen and antibody anti-mesothelin antibodies conjugated with cytotoxins such as PE, DT, ricin and abrin for inhibiting the growth of tumor cells bearing mesothelin. Therefore, it would have been obvious to one of ordinary skill in the art to efficiently increase the affinity of the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$, dsFv) by targeting mutations to CDR hot spots and away from residues that may destroy the structural scaffold and hence, its antigen-binding function and one of ordinary skill in the art would have been motivated to increase the affinity for increased tumor targeting and retention for therapeutic benefit of mesothelin expressing tumors. Thus, it would have been obvious to one skilled in the

art at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$, dsFv) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of claims 1-7 and 9-31 of U.S. Patent No. 6,809,184 B1 and Chowdhury et al and Wagner et al and Schier et al and Pastan et al.

18. Claims 1-6, 8-21, 33-34, 51-54, 56-59, 64 and 66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of U.S. Patent No. 6,083,502 in view of Chowdhury et al (Proc. Natl. Acad. Sci. USA 95: 669-674, January 1998, cited previously on PTO-892 mailed 11/6/03) and Wagner et al (Nature 376: 732, 31 August 1995, cited previously on PTO-892 mailed 11/6/03) and Schier et al (Journal of Molecular Biology, 263:551-567, 1996) and Queen et al (U.S. Patent 5,530,101, 6/25/1996).

The instant claims and their interpretation have been described supra.

Claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of U.S. Patent No. 6,083,502 are drawn to a method of delivering an effector molecule to a tumor cell expressing mesothelin and a method of impairing growth of a tumor cell expressing mesothelin comprising contacting said mesothelin expressing cell with a chimeric molecule comprising a targeting molecule that binds to a portion of mesothelin that is not recognized by monoclonal antibody K1, wherein the targeting molecule is an antibody or

a scFv that binds mesothelin and wherein the tumor cell is an ovarian tumor cell and the effector molecule is a cytotoxin, a label, a radionuclide or a drug and the cytotoxin is selected from *Pseudomonas* exotoxin, ricin, abrin, and Diptheria toxin. Further, the claims are drawn to a chimeric molecule comprising a targeting molecule and an effector molecule, wherein the targeting molecule binds to a portion of mesothelin that is not recognized by monoclonal antibody K1 and the effector molecule is a cytotoxin that is *Pseudomonas* exotoxin and a kit comprising said chimeric molecule and pharmaceutical compositions comprising said chimeric molecule and a pharmaceutically acceptable carrier and a monoclonal antibody that binds to a portion of mesothelin that is not recognized by monoclonal antibody K1. Applicant is reminded that the intended use of the kit for the detection of tumor cells expressing mesothelin is given no patentable weight (MPEP 2111.02). The claims in U.S. Patent No. 6,083,502 do not specifically teach an antibody having 5 times greater affinity for mesothelin, wherein the antibody has a sequence that differs from the parental antibody by an amino acid substitution of at least one amino acid in a CDR hot spot (AGY or RGYW). This deficiency is made up for in the teachings of Chowdhury et al and Wagner et al and Schier et al and Queen et al.

Chowdhury et al have been described supra Chowdhury et al also teach that mesothelin is a differentiation antigen expressed on the surface of ovarian cancers, mesotheliomas and several other types of human cancers (see abstract) and antibody SS (scFv) binds a different epitope from that of antibody K1 (see page 671, right column and Figure 2).

Wagner et al have been described supra.

Schier et al have been described supra.

Queen et al teach monoclonal antibodies for human therapy as well as antibody fragments such as Fv, Fab, and F(ab)2 (column 11) and pharmaceutical compositions comprising an antibody and a pharmaceutically acceptable carrier and the antibody may be conjugated to a cytotoxic agent including a radionuclide, a chemotherapeutic drug, a label and cytotoxic proteins including pokeweed antiviral protein, Pseudomonas exotoxin, ricin or diphtheria toxin (see columns 19-20) and kits comprising the antibody as well as intravenous administration of the antibody composition (see columns 23-24).

The claims in the instant application are obvious variants of claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of U.S. Patent No. 6,083,502 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury

et al and Wagner et al and Schier et al and Queen et al because Chowdhury et al teach that the SS scFv binds with high affinity to mesothelin and SS scFv-PE38 immunotoxin kills mesothelin expressing cells and produced regressions of mesothelin-containing tumors whereas other anti-mesothelin antibodies with low affinity and poor internalization (i.e., mAb K1) were not useful for targeted therapy and Wagner et al teach hot spot motifs AGY and [A/G,G, C/T,A/T] and hot spot mutations are targeted to residues that could yield increased affinity and are away from sites that are more likely to destroy the structural scaffolding and Scheir et al teach that in vitro affinity maturation of an antibody fragment (c-erbB-2 scFv) was observed to mimic somatic hypermutation in vivo, which targets specific sequence hot spots intrinsic to the mutational process and this affinity maturation yielded affinities in the low nanomolar range or lower (i.e., picomolar). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of Chowdhury et al and Wagner et al and Schier et al and Queen et al because Queen et al teach monoclonal antibodies and immunotoxins for human therapy and antibody fragments such as Fv, Fab, and F(ab)2 and pharmaceutical compositions comprising an antibody/immunotoxin and a pharmaceutically acceptable carrier as well as kits comprising the antibody/immunotoxin and intravenous administration of the antibody composition for immunotherapy. Therefore, it would have been obvious to one of

ordinary skill in the art to efficiently increase the affinity of the SS scFv or other anti-mesothelin antibodies (i.e. Fab, $F(ab)_2$) by targeting mutations to CDR hot spots and away from residues that may destroy the structural scaffold and hence, its antigen-binding function and one of ordinary skill in the art would have been motivated to increase the affinity for increased tumor targeting and retention for therapeutic benefit of mesothelin expressing tumors. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have only mutated CDR hot spots in the SS scFv or other anti-mesothelin antibodies (Fab, $F(ab)_2$) to efficiently increase antibody affinity, avoid deleterious mutations and increase tumor retention for therapeutic benefit of tumors expressing mesothelin in view of claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of U.S. Patent No. 6,083,502 and Chowdhury et al and Wagner et al and Schier et al and Queen et al.

Claims 1-6, 8-21, 33-34, 51-54, 56-59, 64 and 66 are directed to an invention not patentably distinct from claims 1-7, 9-14, 18, 20, 24, 26 and 30-31 of commonly assigned U.S. Patent No. 6,083,502. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 6,083,502, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35

U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusions

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
5/25/05